REMARKS

A. Examiner Interview

On May 19, 2006 Applicants' representative, Kenneth Jenkins, spoke with the Examiner regarding the outstanding final Office Action. During the interview, the Examiner requested that Applicants submit a response to the Final Office Action summarizing the remarks previously submitted. The Examiner stated that, upon receipt of the response to the Final Office Action, the finality of the rejection would be withdrawn and a new non-final office action would be prepared and sent to Applicants.

Therefore, as requested by the Examiner, below is a summary of the remarks previously submitted. Applicants look forward to receiving the non-final action promised by the Examiner in due course.

Applicants thank the Examiner for her time and courteousness in the Interview of May 19, 2006.

B. Status of the Claims

Claims 25-27 are pending and stand rejected.

C. Rejection under 35 U.S.C. §103(a)

Claims 25-27 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Nichols et al., U.S. Patent Number 5,099,005 in view of Zuk et al., U.S. Patent Number 4,281,061. Applicants respectfully disagree because:

(1) Neither Nichols nor Zuk teach the use of an N-glycosidase or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid to produce $F(ab')_2$ fragments;

(2) Nichols ***teaches away*** from the use of an N-glycosidase and an O-glycosylase; and

(3) None of the cited references provide a suggestion to modify the methods of Nichols to employ an N-glycosidase and/or an O-glycosylase capable of

hydrolyzing a glycosidic linkage between a sugar unit and an amino acid for the purpose of producing $F(ab')_2$ fragments.

1. The Art of Record Fails to Teach Each Claim Element

Claim 25 encompasses a kit for making $F(ab')_2$ fragments from a glycosylated antibody. The kit of claim 25 includes "a deglycosylation composition comprising at least one glycosidase capable of catalyzing the hydrolysis of an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid to form a partially or wholly deglycosylated antibody." Therefore, to meet all the elements of claim 25, the cited combination of references must minimally teach the treatment of a glycosylated antibody with an N-glycosidase and/or an O-glycosylase capable of cleaving an antibody glycan at the amino acid to which the glycan is attached for the purpose of producing $F(ab')_2$ fragments.

Nichols fails to teach the use of an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid to produce $F(ab')_2$ fragments. Rather, Nichols specifically teaches that antibodies should be treated with a ***sialidase only*** to remove the terminal sialyl residues of the antibody oligosaccharides. The specification repeatedly refers to the desialylation step and the production of desialylated antibodies as a necessary component of the invention and not merely an embodiment of the invention. *See* column 2, lines 40-52; column 5, lines 26-28; and Abstract.

It is well known in the art that sialidases (also referred to as neuraminidases) specifically hydrolyze the glycosidic bond between a sialic acid and a sugar unit, and not between a sialic acid and an amino acid. *See* JM Lackie & JAT Dow (1999) "The Dictionary of Cell & Molecular Biology" (Third edition), Academic Press, London. (ISBN 0-12-432565-3); *see also* http://www.biochem.ucl.ac.uk/bsm/enzymes/ec3/ec02/ec01/ec0129/ describing functional activity of endo-alpha sialidase. Thus, a sialidase is not "capable of catalyzing the hydrolysis of an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid to form a partially or wholly deglycosylated antibody " as recited in claim 25.

Because neither Nichols nor Zuk describe production of $F(ab')_2$ fragments using a deglycosylation composition comprising "at least one glycosidase capable of catalyzing the

hydrolysis of an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid," a proper *prima facie* case of obviousness cannot be set forth. Therefore, Applicants respectfully request withdraw of the rejection under 35 U.S.C. § 103.

2. There is No Reasonable Expectation of Success: Nichols Teaches Away from the Claimed Invention

Applicants respectfully assert that the cited references provide no reasonable expectation of successfully using an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid for the purpose of producing $F(ab')_2$ fragments. In fact, Nichols ***teaches away*** from the use of glycosidases other than sialidases.

Nichols teaches that ***only a sialidase*** is capable of enhancing the yield of $F(ab')_2$ fragments. At column 6, lines 27-45, Nichols explain the basis for the yield enhancement of $F(ab')_2$ fragments after treatment with a sialidase:

> After desialylation of intact immunoglobulin, however, the desialylated immunoglobulin has heavy chains exhibiting the same or substantially similar molecular weight, and therefore both heavy chains and both light chains of the immunoglobulin will be exposed to the proteolytic enzyme affecting the fragmentation reaction to the same extent. As a result, the yield of the desired fragment is expected to increase.

Thus, Nichols teach that the key to $F(ab')_2$ yield enhancement is the production of immunoglobulin heavy chains exhibiting substantially the same molecular weight. At column 5, lines 26-34, Nichols explicitly teach that ***only desialylation and not deglycosylation*** produces heavy chains of the same molecular weight:

> This yield enhancement method exploits the observation that the differences in immunoglobulin heavy chain molecular weight are attributable to ***asymmetric sialylation*** of the heavy chains, ***rather than asymmetric glycosylation*** thereof.

Here, Nichols state that asymmetric glycosylation is not the cause of differences in the molecular weights of the heavy chains. Thus, after examining the above passages, one of skill would

necessarily conclude that the use of a deglycosylating enzyme other than a sialidase would produce heavy chains of substantially different molecular weight leading to a difference in heavy chain protease fragmentation, and ultimately resulting in poor $F(ab')_2$ production. Therefore, Nichols teaches away from the use of a deglycosylation composition comprising "at least one glycosidase capable of catalyzing the hydrolysis of an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid."

Because Nichols teaches away from the use of glycosidases other than sialidases, the cited references provide no reasonable expectation of successfully producing $F(ab')_2$ fragments using an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid.

3. There is No Suggestion to Modify the Reference Teachings

At present, there are no references of record that either expressly or impliedly contain a suggestion to modify the methods of Nichols to employ an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid to produce $F(ab')_2$ fragments as recited in the claims. Nichols does not suggest that there is any deficiency in the disclosed methods that could be remedied by replacing or combining a sialidase with an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid to produce $F(ab')_2$ fragments. The only suggestion to use an N-glycosidase and/or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid to produce $F(ab')_2$ fragments is found within Applicants' own specification.

Therefore, Applicants respectfully submit the there is no suggestion to modify the method of Nichols to obtain a kit for producing $F(ab')_2$ fragments containing an N-glycosidase or an O-glycosylase capable of hydrolyzing a glycosidic linkage between a sugar unit and an amino acid.

D. Double Patenting Rejection

Claims 25-27 stand rejected under the judicially created doctrine of double patenting over claims 1-9 of U.S. Patent No. 6,720,165. Applicants request that this rejection be

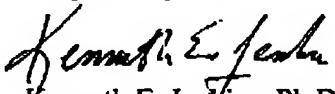
held in abeyance until allowable subject matter is found, at which point appropriate action will be taken to obviate the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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